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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/465,491	12/16/1999	Sheng-Yung Pai Chang	RPA1002	8931

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EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/465,491	Applicant(s) CHANG ET AL.	
	Examiner Jeanine A Goldberg	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,28-33 and 35-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,28-33 and 35-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed September 27, 2002. Currently, claims 21, 28-33, 35-49 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

2. Any objections and rejections not reiterated below are hereby withdrawn.

3. This action is FINAL.

New Matter

4. Claims 21, 28-33, 35-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to a primer pair where the first primer hybridizes within exon 8 and the second primer "hybridizes within, upstream or downstream of exon 8 of the hTERT" are included (Claim 21, 38, for example). The specification does not describe or discuses second primer "hybridizes within, upstream or downstream of exon 8 of the hTERT". Instead the specification describes amplification primers which amplify using a pair of primers comprising a "primer that hybridizes within exon 8 and a primer that hybridizes either upstream of exon 7 or downstream of exon 8" (page 15-16). This description does not support second primer "hybridizes within, upstream or downstream of exon 8 of the hTERT". For example, the specification does not discuss or disclose a primer pair where both primers are within

exon 8; a primer pair where a primer is in exon 8 and in exon 7. The claim encompasses these limitations which are not disclosed. The concept of "second primer "hybridizes within, upstream or downstream of exon 8 of the hTERT" does not appear to be part of the originally filed invention. Therefore, "second primer "hybridizes within, upstream or downstream of exon 8 of the hTERT" constitutes new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 38-45, and Newly Added Claims 48-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kilian et al (Human Molecular Genetics, Vol. 6, No. 12, pg. 2011-2019, 1997) in view of Nakamura et al (Genbank Accession Number AF015950, August 1997) and in further view of Stratagene Catalog (1988).

This rejection is directed to kit claims containing primer pairs.

It is noted that these claims contain a preamble which recites an intended use, however, it is also noted that this use does not confer patentable weight on the product claims since the preamble does not materially change what is present in the kit itself and thus represents an intended use of the kit (see MPEP 2111.02). Further, with regard to the limitation that the kits contain instructions for identifying cancerous cells,

the inclusion of instructions is not considered to provide a patentable limitation on the claims because the instructions merely represent a statement of intended use in the form of instructions in a kit.

Kilian et al. (herein referred to as Kilian) teaches the beta deletion in the hTCS1 gene (also referred to as hTERT, see specification pg. 1). Kilian teaches that the beta-exon deletion encode truncated proteins. Kilian teaches regions surrounding the beta-exon deletion region (see Figure 5). Kilian teaches numerous oligonucleotide primers which include HT2356R. HT2356R is located within exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4. Kilian teaches that hTCS1 is differentially expressed in normal and tumor tissues. As seen in Figure 4, TR-PCR was carried out on RNA with primer combinations including HT2356R (limitations of Claim 3). Kilian teaches southern and Northern analysis using P-labeled probes, RT-PCR analysis using electrophoresis in a agarose gel and probing with a radiolabeled oligonucleotide (pg 2017, col. 2). Finally, Kilian teaches that the beta-exon deletion encodes a truncated protein.

While Kilian teaches a primer which is located in exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4, neither Hudkins nor Kilian specifically teach the primers and probes of the instant case in a kit.

Nakamura however teaches the entire sequence of the hTERT gene.

Stratagene teaches gene characterization kits.

Additionally, in the recent court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the court determined that the existence of a general method of identifying a

specific DNA does not make the specific DNA obvious. Regarding structural or functional homologues, *however*, the court stated

> "Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologues because homologues often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers simply represent functional equivalents of the full length disclosed hTERT sequence concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers and probes are *prima facie* obvious over the cited reference in the absence of secondary considerations. Designing primers and probes which are equivalents to those taught in the art is routine experimentation. The ordinary artisan would have been motivated to have designed probes and primers based upon the sequence of Nakurma which were functional equivalents to those provided by Kilian. Given the primers taught in the art, namely HT2026F and HT2356R of Kilian, the ordinary artisan would have been motivated to have modified the primers of Kilian to obtain functional equivalents. The art provides the sequence of the entire hTERT gene which allows the ordinary artisan to obtain equivalent primers. With regard to structural similarity, the primers of Kilian and the primers of the instant invention are both positioned region suggested by applicant as ideal, namely in the B-deletion, specifically exon 8, and upstream of the B-deletion. Thus, the primers have the same function to amplify the hTERT gene, in the same region, such that the primers would be expected to amplify only nucleic acids

which lacked the deletion of exon 7 and 8, the B-deletion. One of ordinary skill in the art would have had a reasonable expectation of success of obtaining equivalent primers to those of Kilian i.e., the sequence for the complete gene was known, desire to select primers in this region is taught by Kilian, parameters which effect primer annealing and specificity of amplification were well known in the art. It is routine experimentation to obtain additional primers having the same functional properties as the primers claimed.

For the convenience and clarity of the issue, the following diagram has been provided to illustrate the positioning of the primers of Kilian and the instant application.

2101 cctggacgatatccacagggcctggcgcaccttcgtgctgcgtgtgcgggcccaggaccc
2161 gccgcctgagctgtacttgtcaaggtggatgtgacgggcgcgtacgacaccatccccca
2221 ggacaggctcacggaggtcatcgccagcatcatcaaaccccagaacacgtactgcgtgcg
2281 tcggtatgccgtggtccagaaggccgcccatgggcacgtccgcaaggccttcaagagcca
2341 cgtctctaccttgacagacctccagccgtacatgcgacagttcgtggctcacctgcagga
2401 gaccagcccgctgagggatgccgtcgtcatcgagcagagctcctccctgaatgaggccag
2461 cagtggccgctccgaagtctccatccgctcatgtgccaccacgccgtgcgcatcagggg
2521 caagtcctacgtccagtgccaggggatcccgcagggctccatcctctccacgctgctctg
2581 cagcctgtgctacggcgacatggagaacaagctgtttgcggggattcggcgggacgggct
2641 gctcctgcgtttggtggatgatttcttgttggtgacacctcacctcacccacgcgaaaac

The primers highlighted are the primers taught in the art, namely Kilian Primer HT2026F and HT2356R. The primers underlined are the primers taught in the instant specification, namely SEQ ID NO: 2, 4 and 5. It is clear that both the specification and the art teach a primer pair which contains one primer within exon 8, within the B-deletion, and the second primer upstream of exon 7, outside of the B-deletion. Absent factual evidence that the instant primers have unexpected benefits or properties such that they would not be equivalents to those provided in the art, the claimed primers are

merely functional equivalents of the primers provided in the art for amplifying the hTERT gene.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the primers of Kilan for detection of hTERT mRNA since the entire hTERT sequence was taught and characterized by Nakamura and placed the primers and probes into a kit. The ordinary artisan would be motivated to have packaged the primers into a kit to reduce waste, save money, increase quality control and save time, as taught by Stratagene.

Response to Arguments

The response traverses the rejection. The response asserts that neither Kilian, Stratagene or Nakamura alone or in combination teach or suggest that hTERT mRNA comprising a B-region coding sequence is an accurate marker for telomerase activity. This argument has been reviewed but is not convincing because the in kit claims, product claims, the intended use does not carry patentable weight. Thus for the reasons above and those already of record, the rejection is maintained.

Allowable Subject Matter

Claims 21, 28-33, 35-37, 46-47 are drawn, in part, to methods of identifying the presence of cancerous cells in a human sample by determining the quantity of hTERT mRNA comprising B-region coding sequences in sample and non-cancerous cells using a primer pair within exon 8 and a primer pair either upstream of exon 7 or downstream

of exon 8 wherein greater quantity of hTERT mRNA comprising the B-region coding sequence is indicative of cancer cells.

The art teaches the identification of B-deletion and the relationship between quantity of hTERT mRNA and cancerous cells. Kilian teaches the beta deletion in the hTCS1 gene (also referred to as hTERT, see specification pg. 1). Kilian teaches numerous oligonucleotide primers which include HT2356R. HT2356R is located within exon 8 and overlaps the last 7 nucleotides of SEQ ID NO: 4.

Hisatomi teaches that levels of hTERT mRNA was investigated with regard to tumor tissue and non-cancerous tissues. The difference of hTERT mRNA level was highly significant between the tumor tissue and the non-cancerous liver tissue (abstract). Moreover, a strong correlation between the levels of hTERT mRNA and that of telomerase activity in HCC was observed (abstract). HTERT mRNA was amplified using primers within exon 3 and 4, a real-time PCR system provided the essential information to quantify the initial target copy number (pg 728, col. 1-2). As seen in Figure 4, a correlation between the quantification of hTERT mRNA and telomerase activity is provided such that telomerase activity may be assessed from the mRNA of hTERT (limitations of Claim 8). Hisatomi teaches that there were significant correlations between the levels of hTERT mRNA and that of telomerase activity (r=0.751) in tumor tissues (abstract).

The response filed June 18, 2001 provides that the claimed methods provide an accurate and reproducible measure of telomerase activity by selectively measuring mRNA that encodes an active hTERT protein. Given the comparison of the results of

Example 4 and 5 to results of Hisatomi, the methods of the instant application appear to demonstrate unexpected results in a significantly more accurate measure of telomerase activity. The instant specification teaches the r2 of over 96% indicates that using the hTERT mRNA as a predictor of telomerase activity provides an accurate measure of telomerase activiy (page 36). Example 7 demonstrates that using the TaqMan assay described above, normal tissue and tumor tissue samples were different (page 38-39).

The correlation coefficient= 0.751 of Hisatomi is less of a correlation than with the instant methods which demonstrate a high correlation (correlation coefficient =0.9805) (page 14 of response filed June 18, 2001). The response further asserts that "the primary distinction between the methods is the primers used, the results demonstrate that the improvement results from the primers used" (page 14 of response filed June 18, 2001). Therefore, method claims directed to the unexpected benefits of the primers are allowable over the art.

Conclusion

6. No claims allowable.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Goldberg
December 3, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600